UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY and MANULIFE INSURANCE COMPANY, Plaintiffs, v. ABBOTT LABORATORIES, Defendant.	CIVIL ACTION NO. 05-11150-DPW

ABBOTT'S DEPOSITION DESIGNATIONS AND COUNTER DESIGNATIONS FOR BRUCE RODDA

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached deposition designations and counter-designations for the June 6, 2007 deposition of Bruce Rodda, Ph.D., Clinial Trials and Statistics Expert.

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Dated: February 18, 2008

Respectfully submitted,

ABBOTT LABORATORIES

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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

/s/ Ozge Guzelsu

Bruce Rodda Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
6/6/2007	Rodda, Bruce	18:21-19:4					
6/6/2007	Rodda, Bruce	50:3-50:15	49:21-50:2				
6/6/2007	Rodda, Bruce	50:21-52:19	52:20-53:13				
6/6/2007	Rodda, Bruce	53:20-54:3	54:14-54:17				
6/6/2007	Rodda, Bruce	55:2-55:8	55:9-55:15				
6/6/2007	Rodda, Bruce	56:4-57:15	58:19-59:22				
6/6/2007	Rodda, Bruce	60:14-60:24					
6/6/2007	Rodda, Bruce	63:15-63:25					
6/6/2007	Rodda, Bruce	64:5-64:21	67:22-68:12				
6/6/2007	Rodda, Bruce		72:16-75:20				
6/6/2007	Rodda, Bruce	72:6-72:15	76:20-78:14				
6/6/2007	Rodda, Bruce		80:17-81:2				
6/6/2007	Rodda, Bruce	80:9-80:16	82:19-85:15				
6/6/2007	Rodda, Bruce	85:16-85:24					
6/6/2007	Rodda, Bruce	87:10-87:13	87:14-88:15		6	ES	
6/6/2007	Rodda, Bruce	88:16-88:25			6	ES	
6/6/2007	Rodda, Bruce	90:11-90:22	90:23-91:13		6	ES	

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
6/6/2007	Rodda, Bruce		93:1-93:17				
6/6/2007	Rodda, Bruce		94:11-94:14				
6/6/2007	Rodda, Bruce		94:19-95:16				
6/6/2007	Rodda, Bruce	95:17-95:25	96:1-96:20				
6/6/2007	Rodda, Bruce	100:3-100:5					
6/6/2007	Rodda, Bruce	110:16-110:24					
6/6/2007	Rodda, Bruce	112:4-113:8	113:9-113:21		2		
6/6/2007	Rodda, Bruce		114:5-115:10				

Color Key to Deposition Designations


Designation by Plaintiffs


Counter Designation by Defendants


Designation by Defendants

THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE)
COMPANY, JOHN HANCOCK VARIABLE)
LIFE INSURANCE COMPANY AND)
MANULIFE INSURANCE COMPANY)
F/K/A INVESTORS PARTNER)
INSURANCE COMPANY)
)
Plaintiff,)
)
VS.) CIVIL ACTION NO:
) 05-11150-DPW
ABBOTT LABORATORIES,)
)
Defendant.)

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ORAL/VIDEO DEPOSITION OF

BRUCE RODDA, Ph.D.

JUNE 6, 2007

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HIGHLY CONFIDENTIAL

ORAL DEPOSITION OF BRUCE RODDA, Ph.D., produced as a witness at the instance of the Plaintiff, was duly sworn, was taken in the above-styled and numbered cause on the JUNE 6, 2007, from 9:00 a.m. to 2:50 p.m., before Chris Carpenter, CSR, in and for the State of Texas, reported by machine shorthand, at the Longhorn Conference Room, Austin Airport Marriot South, 4415 S. IH-35, Austin, Texas, pursuant to the Federal Rules of Civil Procedure and the provisions stated on the record or attached hereto.

testimony cause you to change any of the opinions you expressed in your -- what I'll call your statistical report?

A. No, it did not.

Q. And just for ease, I'll refer to your rebuttal to Dr. Fairweather as your statistical report and your rebuttal to Dr. Gold as your non statistical report; is that okay?

A. Sure. Yes.

Q. Did reviewing Dr. Gold's deposition transcript cause you to change any of the opinions that you expressed in your non statistical report?

A. No, it did not.

Q. When were you engaged by Munger, Tolles & Olson in this matter?

A. Earlier this year.

Q. In 2007?

A. I think so.

Q. Who engaged you; which attorney?

A. Mr. Phillips.

Q. What tasks did Mr. Phillips ask you to do when he engaged you?

A. The primary task was to effectively be the external statistical expert on 594, reviewing Dr. Gold's and Dr. Fairweather's initial documents and other

documents associated with this trial from a statistical perspective.

Q. Is that it?

A. Yes.

Q. Was this engagement the first time you had ever worked with the law firm of Munger, Tolles & Olson?

A. Yes, it was.

Q. What is your understanding about how Munger, Tolles & Olson identified as you an appropriate expert for this case?

A. Mr. Phillips told me that I was recommended by an individual at Abbott.

Q. Who was that?

A. I don't know.

Q. Have you done work for Abbott before?

A. No.

Q. Do you presently have any equity or other interest position in Abbott?

A. No, I don't.

Q. Have you at any time during the course of your engagement?

A. No.

Q. Your present rate in this matter is how much?

A. $350 a hour.

Q. And from the time you were engaged until today,

companies at which you worked, you would agree that companies evaluate the likelihood of regulatory approval in determining whether to pursue development of drugs, wouldn't you?

A. Yes.

Q. And you would agree, based on your experience, that companies evaluate the results of clinical trials in deciding whether or not to pursue development of drugs, right?

A. That's correct.

MR. ZWICKER: Greg, we've been going an hour. You want to take five?

MR. PHILLIPS: Sure.

MR. ZWICKER: Okay, let's do that. I'm about to move into a new area.

VIDEOGRAPHER: We're off the record at 10:05 a.m.

(recess.)

VIDEOGRAPHER: We're back on the record at 10:16 a.m.

Q. (BY MR. ZWICKER) Dr. Rodda, from a statistical standpoint, can you define the phrase "power" for me?

A. Power is the probability that a study will be statistically significant --

Q. Your words, not mine.

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A. I apologize.

-- given some assumptions.

Q. In the world of statistics, power is known as a planning tool, correct?

A. Primarily, yes.

Q. What does it mean to say that power is a planning tool?

A. The way I define power, the probability of observing a statistically significant result at the end of the study is used to design a study with certain assumptions and certain sample size so that there will be an understood assurance of success. And by success, I mean a statistically significant difference between the treatment and placebo, if there just an active and control agent in the study.

MR. ZWICKER: Okay. Let's go off the record.

(Brief recess).

VIDEOGRAPHER: We're back on the record at 10:18 a.m..

Q. (BY MR. ZWICKER) Dr. Rodda, is it fair to say that power is a way of maximizing the likelihood that the results of a study will show a statistically significant difference between a drug treatment and placebo; is that accurate?

MR. PHILLIPS: Objection to the form.

A. Power is the probability of seeing a statistically significant difference between an active and a placebo.

Q. Why is -- why is it important to design trials with a probability of detecting a difference between treatment and placebo?

A. Studies are an investment, both financial and in patients. When one begins a study, when one embarks on a study, it is important to understand the risks associated with the study. The study can fail for a variety of reasons. There's no guarantee that any study will be positive. There's -- and power is used to create an index so that the sponsor understands the probability that the study will be a success, given some assumptions.

Q. Would you agree that it's a way of maximizing your probability of a conclusive result?

MR. PHILLIPS: Object to form.

A. I would not use the term maximize. I would use the term quantify.

Q. (BY MR. ZWICKER) Fair to say that you testified that clinical trials are expensive, correct?

A. Correct.

Q. So the sponsor hopes to design a study that

will have a high probability of detecting a desired difference between treatment and placebo, fair?

MR. PHILLIPS: Object to the form.

A. In general, yes.

Q. (BY MR. ZWICKER) And one of the reasons for that objective on behalf of a sponsor like Abbott is you don't want to have to repeat a study, right?

MR. PHILLIPS: Object to the form.

A. Yes.

Q. (BY MR. ZWICKER) In your experience, does -- can repeating studies delay development of compounds?

A. Yes.

Q. You've reviewed several documents relating to the 99-114 study in preparation for today, correct?

A. I have.

Q. One of the goals of the 99-114 study was to detect statistically significant difference between treatment groups and placebo; is that fair?

A. Yes.

MR. PHILLIPS: Object to the form.

Q. (BY MR. ZWICKER) Is it your understanding that Abbott's objective was to detect a difference or effect size of .46?

A. Yes.

Q. Can you explain to me what that means?

A. The -- the .46 effect size that Abbott used to design the study was a ratio of the difference in the response of an active group compared with a placebo, divided by the standard deviation. It's a standardized effect size that they used to estimate the size of that study.

Q. But that desired effect was Abbott's objective in designing the study?

A. When Abbott designed the studied, it is my understanding that they identified that as the effect that they wanted to be sure that they found if it were there. And they designed the study to detect that difference or that treatment effect.

Q. In designing the study, Abbott selected a power of 80 percent, correct?

A. That's correct.

Q. What is your understanding of why it is that Abbott selected 80 percent for the 99-114 study?

A. I don't know why they selected 80 percent.

Q. Would you agree with me that sponsors in general like Abbott desire a high probability of a conclusive study?

MR. PHILLIPS: Objection to the form.

A. In general, yes.

Q. (BY MR. ZWICKER) And is it also fair to say

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that power is a way of planning to avoid an inconclusive study? Would you agree with that?

A. I would.

Q. Would you also agree that at least Abbott statisticians determined that 80 percent power in this study would provide sufficiently conclusive results?

MR. PHILLIPS: On object to the form.

A. I don't know who at Abbott decided whether 80 percent power was appropriate.

Q. (BY MR. ZWICKER) But you agree that Abbott institutionally made that determination in designing this study, correct?

A. Apparently.

Q. Putting aside oncology drugs, have you ever designed a study, a clinical trial study at less than 80 percent power?

A. Yes.

Q. Have you ever designed a clinical trial for a pain drug like 594?

MR. PHILLIPS: Object to the form.

A. Yes.

Q. (BY MR. ZWICKER) How many times?

A. In this particular indication, probably three times in this particular indication.

Q. What you do mean by particular indication?

A. Diabetic neuropathy.

Q. And for those three studies that you designed, did you select a power below 80 percent?

A. No.

Q. More than 80 percent?

A. In one case.

Q. And 80 percent in the other two?

A. I think so.

Q. Why did you select 80 percent or more in the three that you designed?

A. The selection of power is not an individual's selection; it is a strategic decision by the company. So in my case, this was a decision that was reached by all the parties that were responsible for the design of the study.

Q. But that strategic decision was informed by a desire to have a conclusive result from the study, true?

A. Yes.

Q. You used the phrase "sample size" a few moments ago. In order to design a study with 80 percent power to show a .46 effect, Abbott would have had to determine a sample size, correct?

A. Correct.

Q. What is a sample size?

A. A sample size is the number of patients that

are assigned to a each of the treatment groups or the totality of the patients that are included in all of the treatment groups.

Q. In your opinion, Dr. Rodda, why is it important in designing a clinical trial to select a proper sample size?

MR. PHILLIPS: Object to the form. Vague as to "proper."

A. The selection of a proper sample size provides the sponsor with an understanding of their risk of success and failure to find a particular treatment effect. If the -- if they use too few patients, that likelihood would decrease. If they use to too many patients, they may be spending money and exposing patients unnecessarily.

Q. (BY MR. ZWICKER) So sponsors prefer to find the right balance; is that fair?

A. That's correct.

Q. One of the risks of selecting too few patients for a sample size is a risk that you might have to repeat the study again, true?

MR. PHILLIPS: Object to the form.

A. That's one of the risks.

Q. (By MR. ZWICKER) What are the others?

A. That you may not be able to repeat the study or

the study may turn out to be negative.

Q. How do you mean negative?

A. Inconclusive.

Q. By inconclusive, you mean that it doesn't show, for the purposes the 99-114 study by example, it doesn't show the effect that you hoped it would show when the results are in?

A. By conclusive, I mean that the -- the statistical significance of the outcome is not definitive enough to make the conclusion that the study was designed to make.

Q. And one of the risks of too small a sample size is that you would not be able to draw that conclusion that, fair?

A. That's correct.

Q. In the 99-114 study, Abbott selected 80 percent power, correct?

A. Correct.

Q. And that was a decision that Abbott statisticians made, correct?

MR. PHILLIPS: Objection, asked and answered.

Q. (BY MR. ZWICKER) You can answer.

A. It's a corporate -- it's a sponsor's -- excuse me. It's a strategic decision.

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Q. Did you yourself, in connection with your testimony today, draw -- attempt to calculate a sample size that would have achieved 80 percent power with a .46 effect?

A. Are you asking have I -- did I try to duplicate the Abbott calculations?

Q. Correct, that's what I'm asking.

A. I did do that.

Q. You did or did not?

A. I did.

Q. And what were your results?

A. The same as Abbott's.

Q. Which means what?

A. That assuming a treatment effect of .46 and a power of .8 and an alpha level Type I error level of .05, that the -- that 80 patients per group, their sample size, would provide 82 percent power for finding the .46 effect significant.

Q. As a general statistical matter, if one reduces sample size, is it fair to say that one also reduces power?

MR. PHILLIPS: Objection to the form, incomplete hypothetical.

A. I want to tie some things together. I want to tie power, sample size, treatment effect and

variability, because it's very difficult and perhaps impossible to talk with one without the other.

So to answer your question, if the variability was as hypothesized --

Q. Constant.

A. No. There is a -- in designing the study, there was an assumption of a particular variability, and Abbott did not know what the true variability would be. They couldn't know. So they had to assume that there's a variability in the system to design the study. When the study is actually implemented, that variability may be greater or less than what they thought it was going to be. And the impact of that will be to increase or decrease the probability of success, depending on the greater the variability, the less likelihood of success given the same sample size.

Sample size works the same way. If variability is constant, if we don't think about variability, if we don't think about the treatment effect that we were interested in, increasing sample size increases power. Decreasing sample size decreases power.

Q. Abbott didn't know the actual variability of the 99-114 study until it unblinded the data, right?

A. That's correct.

Q. Before Abbott unblinded the data, it made certain assumptions about variability, correct?

A. I don't know.

Q. Well, variability assumptions, as you said, have an impact on sample size, correct?

MR. PHILLIPS: You have to answer verbally.

THE WITNESS: I'm sorry. I apologize.

MR. ZWICKER: Thank you. That's usually my job.

A. They had to make some assumptions about variability to design the study, to come up with the sample size in the first place.

Q. (BY MR. ZWICKER) Before the results are unblinded and while Abbott's initial assumptions regarding variability are in place, would you agree with me that reducing sample size reduces plan power?

A. It would reduce it if the variability were unchanged from what they hypothesized it would be and that the treatment effect was unchanged from what they hypothesized it would be.

Q. But again, you only know actual variability once you unblind the data, true?

A. True.

Q. You agreed Abbott made certain assumptions

enrollment in the 99-114 study as of December 14, 2000, fair?

MR. PHILLIPS: Objection, mischaracterizes the document.

A. It proposes that the they terminate enrollment.

Q. (BY MR. ZWICKER) Based on your review of documents in this case, you understood that Abbott had a target enrollment of 320, correct?

A. Yes.

Q. And do you also understand, based on your review of documents in this case, that the total number of persons randomized to the 99-114 study ultimately was 266?

A. Yes.

Q. Do you agree that as of the date Abbott reduced enrollment from 320 to 266, that Abbott should have known that plan power would have been reduced?

A. Probably.

Q. Why do you say probably?

A. Because of the other factors that they were unaware of which could have affected the power as well, the treatment difference and the variability.

Q. Okay. But as of December 2000, Abbott doesn't know the variability, right?

A. That's correct.

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Q. This is actually one of those examples of where Mr. Phillips happens to be right, rare but true, that we're speaking over one another.

MR. PHILLIPS: One of many examples.

Q. (BY MR. ZWICKER) And as of December 2000, Abbott hasn't changed the desired effect for the 99-114 study, right?

A. That's correct.

Q. So fair to say that as of December 2000, Abbott should have appreciate that reduction of the sample size from 320 to 266 should reduce plan power, true?

MR. PHILLIPS: Objection to the form.

A. It may reduce plan power.

Q. (BY MR. ZWICKER) But power is a judgment that is made before you actually have results, typically, it's a planning tool, right?

A. That's correct.

Q. So, as of December 2000, Abbott would have to reduce plan power, wouldn't it?

MR. PHILLIPS: Object to the form.

A. I think they -- that's a probable yes.

Q. (BY MR. ZWICKER) What is your understanding, based on documents you reviewed or conversations that you've had with Mr. Phillips, regarding why it was that Abbott reduced the sample size in the 99-114 study?

A. Assuming that the variability and the treatment effect were as they hypothesized, it would have the effect of reducing the power of the study.

Q. (BY MR ZWICKER) And reducing the enrollment size from 320 to 266 effectively reduces the sample size as well, doesn't it?

A. I'm sorry. Would you say that again?

Q. Yes. Reducing the enrollment target effectively has the result of reducing the sample size, doesn't it?

A. I'm sorry. It sounds like a tautology.

Q. Let me try it once more.

Abbott -- Abbott's objective was for a sample size of 320 persons?

A. Correct.

Q. At the time enrollment was terminated, 266 patients were randomized?

A. Correct.

Q. Fair to say that the sample size is now been reduced?

A. Yes.

Q. Do you agree with the proposition that stopping enrollment short of target may result in a study where the treatment difference between the agent and control may not be statistically significant?

MR. PHILLIPS: Object to the form.

A. It may not. But it also may not if you completed the study to full enrollment.

Q. (BY MR. ZWICKER) What do you mean by completed the study to full enrollment?

A. All other assumptions being the same, variability and treatment difference, had the study been conducted through with 320 patients, you would have had a twenty percent chance of an inconclusive result. So the fact that you went through the entire sample, doesn't guarantee that you're going to have a conclusive result.

Q. Okay. But reducing -- terminating enrollment increases the probability that the desired effect may not be statistically significant, true?

MR. PHILLIPS: Objection to the form.

A. It does affect it.

Q. (BY MR. ZWICKER) It increases the probability?

A. It increases the probability.

Q. And by increasing the probability, does reducing the sample size also increase the probability of repeating the trial?

MR. PHILLIPS: Objection to the form. Vague as to increasing the probability of what?

A. I can't answer that question. That would be a

A. No.

Q. You don't know one way or another or you disagree?

A. I don't think it was in the protocol stated that way.

Q. Based on your experience, and putting yourself in Abbott's shoes as of December 2000, is it -- would it be your opinion that the failure to achieve the enrollment target is a potentially important fact in the development of 594?

MR. PHILLIPS: Objection to the form.

A. It could be.

Q. (BY MR. ZWICKER) Why?

A. Because the -- your probability of success is being potentially reduced by reducing the sample size.

Q. Could you turn to page 17 of your report. And by your report, I mean Exhibit Number 2.

You have on page 17, you reproduced a table, and you have a discussion about the implications of terminating enrollment on power, see that?

A. Yes.

Q. You say, "It can be seen from this table that the actual number of patients at the termination of enrollment, 266 or about 65 per group, would provide 74 percent power to detect the hypothesized .46 treatment

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effect compared with an initial power at least 80 percent as cited in the protocol." Do you see that?

A. Yes.

Q. In your opinion, given your review of documents relating to the 99-114 study, do you think a reduction in power from 80 percent to 74 percent is significant?

MR. PHILLIPS: Object to the form.

A. It depends on the corporate objectives, the risk the company is going to take.

Q. (BY MR. ZWICKER) Based on the documents you've reviewed, do you have any opinion regarding the company's view of reducing power from 80 to 74 percent based on cutting the enrollment target?

A. No.

Q. Dr. Rodda, in studies that you've designed, have there been situations where you view a reduction in power of 6 percent to be significant in the development of a compound?

MR. PHILLIPS: Object to the form.

A. No.

Q. (BY MR ZWICKER) In other words, I want to make sure my question is right, there has never been a situation where you concluded that a reduction of 6 percent was meaningful?

A. Not that I can recall.

Q. Why is that?

A. Can I use an example?

Q. Yeah.

A. May I refer to Dr. Fairweather's testimony?

Q. Sure.

A. Recall in that testimony, there was a question of changing the variability by ten percent from 1 to 1.1, increasing the variability by just ten percent. By doing that, the effect on power is exactly the same as reducing the sample size from 320 to 266.

The variability estimates that go into designing a clinical trial are in fact estimates. If the variability is 1 and I estimated it as a .9 or 1.1, that is -- that's pretty accurate. So that the proximations that go into estimating a sample size, if -- if the difference between 1 and 1.1 would make this much difference, then the reduction of a sample size providing an equivalent difference in power, has to be taken with that into consideration.

So, a small decrease in power like this is not something that, in my experience, would have been viewed as being a critical reduction.

Q. Are you saying that for the 99-114 study, Abbott assumed a range of variability in calculating sample size?

A. I don't know that.

Q. Wouldn't you have to know the range of variability assumed in order to assess the impact of a 6 percent reduction in power?

A. No.

Q. Why not?

A. If you -- when interpreting the impact on these reductions in power or changes in variability -- excuse me -- reductions in sample size or changes in variabilities or changes in target treatment effects, these are often compared in pairs to determine the impact of one on the other, and in designing a study, one knows that the estimates are in fact estimates, and sensitivity may be assessed at that time.

There was no evidence in what I read that Abbott wanted to reconsider their variability nor reconsider their treatment effect, but were only interested, given that those had not -- were not changing the impact of their sample size reduction on the power of their study.

Q. So is it your testimony that Abbott assumes certain -- made certain assumptions about variability in the 99-114 study; is that right?

A. Yes.

Q. And what is the relationship between those

variability assumptions and a reduction in power?

A. If the assumed variability is incorrect, if it is too low, then the power will be reduced. If the variability that they assumed is too high and that the true variability is lower, then the power will be increased for the same sample size.

Q. But at this point in December 2000, Abbott as you've testified, doesn't know what the variability is going to be?

A. That's true.

Q. So is Abbott in a position to assess the impact of a reduction in power of 80 to 74 percent without knowing what the variability is going to be?

A. The impact in terms of power?

Q. Yeah.

A. They -- they could speculate what the impact would be with different variabilities.

Q. But they don't know?

A. But they don't know.

Q. Is there a reduction in power in studies you've done that you would consider to be extremely significant in determining whether a study will be conclusive or not?

MR. PHILLIPS: Objection to the form.

A. In general -- in general, no. The concerns

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about lack of enrollment were either for a reason that power then became moot or that the enrollment was acceptable in terms of an adequate power. And adequate is -- I won't define that because it's -- adequate means acceptable to the sponsor in that case.

Q. (BY MR ZWICKER) Would you consider a reduction in power to, say, 65 percent to be significant in the 99-114 study?

MR. PHILLIPS: Object to the form.

A. I think the reduction of power from 82 percent to any point afterward is one that depends on a number of factors, and I would just -- I would be speculating without having knowledge of those factors.

One of the things that I would like to point out is that the reduction of power from 80 percent to 75 percent, say, still means that there's a three-to-one chance that the study will be successful. Reducing it to 67 percent means there's a two-to-one chance that the study will be successful. Those are still high odds, and it would be a corporate decision about where the cutoff point came, where the risk of failure was not worth the benefit.

Q. (BY MR ZWICKER) In your experience, have you planned most clinical trials with 80 percent power?

A. I would say that many late Phase 2 and Phase 3

studies are planned with 80 percent power, but I want to again link the -- the concept of treatment effect and variability, because in many studies the sponsor will say, "We'd like to have 80 percent power and we can afford 100 patients. What difference can we detect?"

So separating power from the treatment effect, they are not separable. They are linked. And you saw the equation in my report. If you change one, you change the others. So you can always fix one. You always fix it to be 80 percent power and then vary your treatment effect, vary your variability, vary your sample size. Now, there's no evidence that Abbott did that. But that's why I want to emphasize you can't just separate power from sample size.

Q. But I think your testimony is that in most of the -- at least initially for the studies that you planned, you selected 80 percent power or better?

A. On many of them, not most of them. Early studies -- early studies are often done with less than 80 percent power.

Q. But Phase 2 trials are mostly done with 80 percent power?

A. Late Phase 2 and Phase 3 trials are usually done with higher powers.

Q. This is a late Phase 2 trial, right?

A. Potentially.

Q. Why only potentially?

A. Because if a patient drops out of a study for a specific reason, for example, tolerability or lack of efficacy, that provides information. And if they drop out, for example, for tolerability reasons, that provides information that may not be attainable if they completed the study.

Q. In your experience, does the FDA consider the reasons why patients drop out of clinical trials?

A. Yes.

Q. What do they look at?

MR. PHILLIPS: Object to the form.

A. They are interested in -- if there is an association for the reason for dropping out and the therapies under study.

Q. (BY MR. ZWICKER) And to the extent that there is an association for the reasons people drop out and the treatment, that's a factor that is not helpful to the development of the compound?

MR. PHILLIPS: Object to the form. I'm not -- object, vague.

A. The purpose of any clinical trial is to characterize both the safety and efficacy. If patients drop out for safety reasons, that is part of the

characterization of the safety profile. Whether it's desirable or not is a different issue.

Q. (BY MR. ZWICKER) For a drug like 594, is it your opinion that the FDA would treat dropouts for adverse effects in a negative way, given the nature of the drug?

MR. PHILLIPS: Objection.

A. I'm not sure what you mean by -- treat in a negative way.

Q. (BY MR. ZWICKER) 594 was a pain drug, correct?

A. Yes.

Q. In your opinion, is the FDA more insistent that pain drugs have fewer adverse effects than other kinds of drugs?

MR. PHILLIPS: Objection, form.

A. I would be speculating about what the FDA feels.

Q. (BY MR. ZWICKER) Okay. But it is your testimony that the FDA does scrutinize the relationship between adverse events and a treatment, correct?

A. Yes, that's true.

Q. You've reviewed the protocol for 99-114, haven't you?

A. I did.

Q. What is -- based on -- well, why don't we mark

PART 8

it.

(Exhibit 5 marked for identification).

Q. (BY MR. ZWICKER) Dr. Rodda, before the witness is the Abbott Laboratories clinical protocol for 99-114, dated February 8, 2000, and bears Bates numbers 65818 through 65896.

Dr. Rodda, do you recognize this as the protocol that you reviewed?

A. Yes.

Q. Take a look at page -- it's 40 of the protocol and it bears Bates Number 65869. Do you see that? It says Data Sets Analyzed?

A. Yes.

Q. Can you review that to yourself and let me know when you're done?

MR. PHILLIPS: Just that one paragraph?

MR. ZWICKER: Just that one paragraph.

A. Okay. I'm done.

Q. (BY MR. ZWICKER) You're done? Can you tell me, based on this protocol, what an intent-to-treat analysis is?

A. An intent-to-treat analysis is designed to include as many patients as possible in the final analysis, so that patients are not excluded for reasons that -- for events that happened to them during the

conduct of the study. The intent-to-treat analysis in general includes all patients randomized to treatment that had any information that addresses the specific objective.

Q. What is the valuable data within the context of this protocol?

A. They have defined their intent-to-treat set as patients who will receive one dose of study drug, had a baseline, and had at least one followup pain assessment.

Q. So based on this protocol, sir, it's your conclusion that the intent-to-treat dataset is the evaluable dataset?

MR. PHILLIPS: Objection, mischaracterizes the testimony.

A. No. No. The dataset -- that evaluable dataset is different. The evaluable dataset requires a week of therapy, seven days of study drug. The intent-to-treat requires one does of study drug.

Q. And both evaluable date and the intent-to-treat datasets are used in analyzing the results once they're known?

A. In general, yes.

Q. Was that true here?

A. They used an intent-to-treat approach and they used an observed-cases approach in their evaluation of

efficacy.

Q. For an intent-to-treat analysis, an intent-to-treat analysis assumes that certain subjects, certain enrolled subjects are going to prematurely terminate, correct?

A. It doesn't assume that. If that happens, then their information will still be included in the analysis. They will not be excluded.

Q. In the intent-to-treat analysis for the 99-114 protocol, is Abbott going to infer data on how the patients would have done had they completed the protocol?

A. Abbott used a technique called last observation carried forward, which imputed the last observation, the last pain observation for patients who dropped out through what -- through their visit schedule, had they completed the study.

Q. So the intent-to-treat analysis at Abbott used for 99-114 imputes data to subjects that prematurely terminate; is that fair?

A. There were -- I think there were two separate analyses, both of which could be called intent-to-treat because they included all the patients, but you're correct in that one of them did impute data for patients who dropped out, efficacy data.

Q. And the other was the safety --

A. The other was the observed cases where data were not imputed but all cases were included, or all the patients defined in the population were included.

Q. So as you say, data was imputed for the efficacy analysis?

A. For one of the efficacy analyses.

Q. The primary?

A. The primary efficacy analysis.

Q. And that's the Likert test, right?

A. That's the variable that was used for the primary variable?

Q. The Likert scale?

A. The Likert scale. It's not a test, it's a scale; it's an evaluation scale.

Q. You would agree with me that you would rather actually, as a sponsor, have the data than impute it for efficacy purposes?

A. I think good science would require that you have as much evaluable data as possible.

Q. I appreciate that, but if given your druthers, wouldn't you rather have actual data from a patient that completed the protocol than imputed data?

A. Yes.

Q. Dr. Rodda, in your report -- actually now I'm

PART 9

agreement that's the subject of this litigation, okay?

A. (Witness nods head yes.)

Q. Would you agree with me that as of March the 12th, 2001, that Abbott knew that roughly half of the enrollees in the 99-114 study had prematurely terminated?

MR. PHILLIPS: Objection to the form.

A. I don't know exactly what they knew at that point.

(Exhibit 6 marked for identification.)

Q. (By MR. ZWICKER) Before the witness is Exhibit Number 6, which is an e-mail and chart that bears Bates numbers 238329 through 238833.

Dr. Rodda, can you review this document and tell me if you recognize it?

A. Yes, I do.

Q. And do you recognize it as one of the documents that was provided to you in connection with your work today?

A. I would have to check the list, but I think so.

Q. Yeah. I'll just represent to you that page 2 of the statistical report indeed lists this document.

A. Thank you.

Q. The date on this document is February 27, 2001, which I'm sure you and Mr. Phillips and I could agree is

before March the 12th, 2001. Do you see that?

A. Yes.

Q. Take a look at page 330.

A. Uh-huh, yes.

Q. And look at the chart there. Do you see Total Randomized as of 1/04?

A. Yes.

Q. It says 269; do you see that?

A. Yes.

Q. That number ultimately became 266, didn't it?

A. Apparently.

Q. And then to the chart to the right, where it says Early Terminations, and it looks like it says as of 2/20, it says 132. Do you see that?

A. I see that, yes.

Q. And then to the right of that, it says Completed Subjects as of 2/20, and then says 130.

A. Yeah.

Q. So based on your review of this document, would you agree with me that as of March the 12th that Abbott knew that roughly -- and I think the early termination number is 49 percent -- that Abbott knew that roughly 50 percent of the enrollees had prematurely terminated?

MR. PHILLIPS: Object to the form.

A. It looks that way, yes.

this table is complete, yes.

Q. (BY MR. ZWICKER) And I'm just going ask you to assume that there are tables that reflect all the patients involved in the study and the dates they terminated.

A. Okay.

MR. PHILLIPS: If that was a question, I'll object to the form.

MR. ZWICKER: Okay. It wasn't, but you can object.

Q. (BY MR. ZWICKER) So you would agree with me that as of February the 27th, Abbott knows that it's not going to have complete data from all 266 enrollees, right?

MR. PHILLIPS: Object to the form.

A. Yes.

Q. (BY MR. ZWICKER) And that it would have to impute under an ITT analysis data for the premature terminations, correct?

A. For one of the ITT analyses.

Q. For the primary efficacy analysis.

A. (Witness nods head yes.)

Q. Dr. Rodda, would you agree with me that for purposes of this study, that having to infer data for roughly half the enrollees potentially increases the

variability around the mean?

A. No -- sorry.

MR. PHILLIPS: I was just objecting to the form.

A. No.

Q. (BY MR. ZWICKER) Why not?

A. If a patient drops out of the study, for example, on day 7, and a value needs to be imputed for the remainder of the study, it's the same number that would be imputed for each of the subsequent visits. It's going to reduce the variability, not increase the variability if the same number is being given through for the remainder of the study.

Q. (BY MR. ZWICKER) When Abbott designed the 99-114 protocol, do you understand that it made -- that it took account for premature terminations in assuming variability?

A. That wasn't clear in the protocol.

Q. You couldn't tell?

A. No.

Q. Would you have expected it to be clear in the protocol?

A. Yes.

Q. Do you have any understanding why an assumption for variability wasn't in the protocol?

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You agreed with me earlier that it's preferable to have someone complete a study than prematurely terminate it, right?

A. The more information that a patient provides, the more valuable that patient is.

Q. Is it problematic to you to treat, under an ITT analysis, to treat the data of a premature terminator and a completer the same way?

MR. PHILLIPS: Object to the form.

A. You are combining patients who provide a substantial amount of information with those who may not, but one approach that Abbott did use was the observed cases approach where all patients data, whether it was in -- was used and there was no imputation. I'm not sure whether that answers your question or not, but let me stop there and let you re-ask the question if I haven't answered it properly.

Q. (BY MR. ZWICKER) For purposes of the 99-114 study, should Abbott have made any adjustments to assumed variability based on the fact that half of the enrollees didn't complete the study?

MR. PHILLIPS: Object to the form. Vague as to time.

Q. (BY MR. ZWICKER) Let me actually address one of his objections. Prior to March the 12th, 2001,

should Abbott have made any adjustments to variability based on the fact that half the persons enrolled in the study didn't complete it?

A. I don't know how they would have.

Q. Why not?

A. I don't know how they would have.

Q. You think they couldn't have?

A. I'm saying that I don't know how you would, even if you wanted to, how you would do that. I don't know of any technique to do that.

Q. Does the fact that Abbott received incomplete data from roughly half the enrollees in the 99-114 study have any impact on the sample size, again, prior to the March 12, 2001?

MR. PHILLIPS: Object to the form.

Q. (BY MR. ZWICKER) Do you understand my question?

A. Let me try to answer it and see whether I do.

The intent-to-treat approach presumes complete data on all patients. So if that is the primary population for analysis, there are effectively no dropouts. And even though much of that data may be imputed, the data is complete. That is, as we -- I testified earlier, that isn't as desirable as having more complete data on individual patients, but Abbott

could view this from the point of view that an intent-to-treat approach was being taken and, because of that, there are few if any dropouts from that analysis, and thus, the sample size is adequate as it is.

Q. In your experience where you have had trials with substantial dropout rates, have you made adjustments to sample size to accommodate for the premature terminations?

A. No.

Q. Why not?

A. For the reason that I gave, is that these were -- these were intent-to-treat analysis primarily, and that with substantial dropouts, the -- well, let me just stop there. That there was no support for increasing the sample size if the information available was addressing the question.

Q. Do you view a 50 percent dropout rate for the study to be substantial?

MR. PHILLIPS: Object to the form.

A. It is a high dropout rate.

Q. (BY MR. ZWICKER) If you were overseeing the study, would you be concerned about the rate of dropouts?

A. I certainly would investigate the rate of dropouts and the reasons for them.

Q. In your experience, have you been able to draw any preliminary conclusions regarding the reasons for dropouts even where data is blinded?

A. No, not where data is blinded.

Q. Do you believe that the power for the 99-114 study should have been further adjusted based on the fact that Abbott knew they had incomplete data from roughly one half of the enrollees?

MR. PHILLIPS: Objection to the form.

A. No.

Q. (BY MR. ZWICKER) Why?

A. According to the protocol, this intent-to-treat approach accommodated all the patients and, therefore, the number of patients who were not part of the intent-to-treat analysis was not as small as the number of patients who completed the study and, therefore, the power would be more associated with the sample size of the 266 patients that were enrolled rather than the 130-something patients that actually completed the study.

Q. (BY MR. ZWICKER) So it's your view that power should not have been further reduced, notwithstanding the fact that data would have to be imputed for roughly half the patients that were enrolled?

A. Abbott could consider that there may be an

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been desirable or not might have been interesting, but I certainly wouldn't have known how to do it.

Q. Will you agree that this was an important study in the development of 594, correct?

A. I think it was.

Q. And would you agree that it was important for Abbott to understand what impact the premature dropout rate had on its objectives for the trial?

MR. PHILLIPS: Objection to the form.

A. I think it was certainly something that they were interested in.

Q. (BY MR. ZWICKER) But based on your review of the records, it's not a calculation they ever undertook, correct?

MR. PHILLIPS: Objection to the form.

A. From what I've seen, they did not calculate the impact of the premature dropouts on the ultimate outcome prior to unblinding.

Q. (BY MR. ZWICKER) Given the importance of the study, is that a calculation that you would have undertaken if you were running this clinical trial, sir?

A. No, I probably wouldn't have.

Q. Why?

A. Two points. One, as I mentioned before, I don't -- I wouldn't know how to do it. And secondly,

and March 12th is 16 days roughly, right?

A. Uh-huh.

Q. Do you believe that within 16 days that Abbott would have known the intent-to-treat population?

MR. PHILLIPS: Objection.

A. I don't know.

Q. (BY MR. ZWICKER) But would you agree -- let's assume that, since you are testifying here as an expert, if Abbott did know the intent-to-treat population as of March 12th, it would know that it had 225 patients to evaluate for the primary efficacy variable, correct?

MR. PHILLIPS: Objection, form.

A. If they did know that -- the intent-to-treat population, then they would know -- would have known that they had 225 patients by their definition.

Q. (BY MR. ZWICKER) It's fair to say that if Abbott's intent-to-treat population was 225, but that's also its sample size for the purpose of the 99-114 study, true?

MR. PHILLIPS: Objection to the form.

Q. (By MR. ZWICKER) For purposes of the primary efficacy?

A. Yes. That was the sample size used in that analysis.

Q. So as of March 12th, Abbott knew that power

knew that its maximum sample size was 225, correct?

MR. PHILLIPS: Objection.

A. They may have.

Q. (BY MR. ZWICKER) And if they did, that would have had an impact on power, true?

MR. PHILLIPS: Objection to the form.

A. It could have.

Q. (By MR. ZWICKER) It would have -- it could have reduced it, correct?

A. It could have.

Q. And assuming that each of the four arms were equally distributed between the four treatment groups, that comes out to roughly 56 persons per arm?

A. (Witness nods head yes.)

Q. True?

A. Yes.

MR. PHILLIPS: Object to the form.

Q. (BY MR. ZWICKER) Go back to exhibit -- go back to your report, which is Exhibit 2 on Page 17 and look at Page 17 of your chart.

A. Uh-huh. Yes.

Q. At a sample size of 55 persons with an effective .46, power to be .67. Do you see that?

A. That's correct. Yes.

Q. In your opinion, is a power of .67 a

significantly lower power than what the study should have had?

MR. PHILLIPS: Object to the form. Incomplete hypothetical.

A. Well, the study was designed for 80 for that difference, so anything less than 80 would be reduced. The actual importance of that again is a decision that's based on other factors rather than just this.

Q. (BY MR. ZWICKER) But would you agree that -- with a plan power of 80 percent and a power of 67 percent as of March 12th, that this study would have been underpowered?

MR. PHILLIPS: Object to the form.

A. Not necessarily.

Q. (BY MR. ZWICKER) Why not?

A. Because if the true treatment difference were greater than .46, it would have been very well powered. If the variability were less than hypothesized, it could have been very well powered. There are knowns that would prohibit me from stating that the study was underpowered.

Q. But you don't know what the true variability is until data is unblinded, correct?

A. Frankly, you never know what the true variability is. You only know what was observed in the

PART 12

study.

Q. But you wouldn't know what was observed in the study until the study is unblinded, correct?

A. True.

Q. And assuming the effect size was .46 -- keep that assumption, okay -- would you agree that if you didn't know what the variability was going to be and you have an effect size of .46, that the study would have been significantly underpowered as a Phase 2B study at 65 percent?

MR. PHILLIPS: 65 percent we're now going to? Objection.

Q. (BY MR. ZWICKER) 67 percent.

MR. PHILLIPS: Objection to the form. I didn't know if that was a trick question. Object to the form.

A. I would conclude that the power was less than 80 percent. I'm loathe to use the term "underpowered." There are too many variables for me to make that conclusion.

Q. (BY MR. ZWICKER) Would you have ever -- have you ever designed a Phase 2B trial with a 67 percent power?

MR. PHILLIPS: Object to the form.

A. I'd like to answer that by going back to a

comment that I made earlier, is that in studies that I've worked on in the past on several occasions, if my client said we would like to find a, for example, a .46 difference with a hundred patients, and I said, well, that would give you 67 percent power, and he said, well, I want 80 percent power, so we change the difference.

So the question -- the power cannot be divorced from the difference -- the treatment effect and the variability. That's why I say that you can -- it's lower, but underpowered is an opinion.

Q. (BY MR. ZWICKER) Okay. If your client came to you and said, "I want .46 effect and a sample size of 225," you would tell them that you would have a 67 percent power?

A. I would say that, yes.

MR. ZWICKER: Why don't we break?

VIDEOGRAPHER: We're off the record at 12:16 p.m.

(Lunch recess.)

THE VIDEOGRAPHER: We're back on the record at 1:10 p.m.

Q. (BY MR. ZWICKER) Good afternoon, Dr. Rodda.

A. Good afternoon.

Q. This morning I think you testified that you couldn't find any adjustment for premature terminations

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July 13, 2007

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VIA FACSIMILE AND U.S. MAIL

Joseph H. Zwicker, Esq.
Choate Hall & Stewart LLP
Two International Place
Boston, MA 02110

Re: John Hancock Life Ins. Co., *et al.* v. Abbott Laboratories

Dear Mr. Zwicker:

Bruce Rodda signed the original transcript of his June 6, 2007 deposition. The corrections made are as follows:

Page/Line Number	Change	Reason
Page 44, line 18	Change "statistic" to "statistics"	Typo
Page 59, line 2	Change "with" to "about"	Clarification
Page 59, line 14	Remove "depending on" and insert "–"	Clarity
Page 62, line 24	After "I think it is." begins Mr. Zwicker's next question.	Correction
Page 63, line 5	Remove "the"	Clarity
Page 64, line 10	Change "appreciate" to "appreciated"	Typo

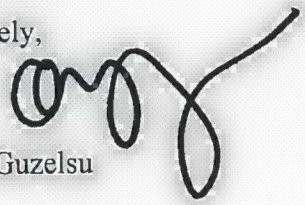
PART 13

Page/Line Number	Change	Reason
Page 64, line 13	Change "plan" to "planned"	Typo
Page 64, line 19	Change "plan" to "planned"	Typo
Page 71, line 1	Remove a "one"	Typo
Page 74, line 15	Change "proximations" to "approximations"	Typo
Page 75, line 18	Replace ", given that those had not -- were not changing" with "in"	Clarification
Page 78, line 10	Remove "always"	Clarification
Page 83, line 18	Change "does" to "dose"	Typo
Page 83, line 19	Change "date" to "dataset"	Typo
Page 84, line 15	After the word "out" insert "as their imputed pain observation for the remainder of the study." Delete lines 16 and 17.	Clarification
Page 92, line 6	Change "given" to "provide"	Clarity
Page 92, line 15	Change "primarily" to "primary"	Typo
Page 93, line 14	Remove ", whether it was in --"	Clarity
Page 97, line 8	Change "equivalence" to "equivalents"	Typo
Page 98, line 2	Change "plan" to "planned"	Typo
Page 98, line 10	Change "plan" to "planned"	Typo
Page 98, line 15	Change "to" to "from"	Clarity
Page 98, line 24	Change "to be" to "be to"	Typo
Page 107, line 13	Replace "as" with "is a"	Typo
Page 107, line 21	Remove "to"	Typo
Page 109, line 4	Replace "leave" with "least"	Typo
Page 113, line 20	Replace "knowns" with "unknowns"	Typo

Page/Line Number	Change	Reason
Page 114, line 18	Replace "loathe" with "loath"	Typo
Page 131, line 10	Delete lines 10 and 11 after the word tolerability and replace with "and adverse events."	Clarification
Page 133, line 13	Insert the word "and" after the word "groups"	Clarity

Copies of the signature page and the errata sheets are included with this letter. Please do not hesitate to call if you have any questions or comments.

Sincerely,



Ozge Guzelsu

cc: Richard C. Abati, Esq. (w/encl.)
Jeffrey I. Weinberger, Esq. (w/encl.)
Gregory D. Phillips, Esq. (w/encl.)
Eric J. Lorenzini, Esq. (w/encl.)
Brian A. Davis, Esq. (w/encl.)
Karen Collari Troake, Esq. (w/encl.)
Andie Cardinale (w/encl.)
Kathy Herrity (w/encl.)

PART 14

SIGNATURE AND CHANGES

RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

PAGE	LINE	CHANGE	REASON
Please see pages 153A, 153B, 153C			

I, BRUCE RODDA, Ph.D., have read the foregoing deposition and hereby affix my signature that same is true and correct, except as noted above.

Bruce Rodda 7/10/07

BRUCE RODDA, Ph.D.

A

SIGNATURE AND CHANGES

RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

PAGE	LINE	CHANGE	REASON
44,	18	Change "statistic" to "statistics"	- typo
59,	2	Change "with" to "about"	- clarification
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62,	24	After "I think it is." begins Mr. Zwicker's next question.	- Correction
63,	5	Remove "the"	- clarity
64,	10	Change "appreciate" to "appreciated"	- typo
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71,	1	Remove a "one"	- typo
74,	15	Change "proximations" to "approximations"	- typo
75,	18	Replace ", given that those had not -- were not changing" with "in"	- clarification
78,	10	Remove "always"	- clarification
83,	18	Change "does" to "dose"	- typo
83,	19	Change "date" to "dataset"	- typo

I, BRUCE RODDA, Ph.D., have read the foregoing deposition and hereby affix my signature that same is true and correct, except as noted above.

Bruce Rodda 7/10/07

BRUCE RODDA, Ph.D.

PART 15

HIGHLY CONFIDENTIAL

B

SIGNATURE AND CHANGES

RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

PAGE	LINE	CHANGE	REASON
84,	15	After the word "out" insert "as their imputed pain observation for the remainder of the study." Delete lines 16 and 17.	- clarification
92,	6	Change "given" to "provide"	- clarity
92,	15	Change "primarily" to "primary"	- typo
93,	14	Remove ", whether it was in --"	- clarity
97,	8	Change "equivalence" to "equivalents"	- typo
98,	2	Change "plan" to "planned"	- typo
98,	10	Change "plan" to "planned"	- typo
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107,	21	Remove "to"	- typo
109,	4	Replace "leave" with "least"	- typo
113,	20	Replace "knowns" with "unknowns"	- typo

I, BRUCE RODDA, Ph.D., have read the foregoing deposition and hereby affix my signature that same is true and correct, except as noted above.

Bruce Rodda 7/10/07

BRUCE RODDA, Ph.D.

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SIGNATURE AND CHANGES

RE: JOHN HANCOCK VS. ABBOTT LABORATORIES

PAGE	LINE	CHANGE	REASON
114,	18	Replace "loathe" with "loath"	- typo
131,	10	Delete lines 10 and 11 after the word tolerability and replace with " and adverse events."	- clarification
133,	13	Insert the word "and" after the word "groups".	- clarity

I, BRUCE RODDA, Ph.D., have read the foregoing deposition and hereby affix my signature that same is true and correct, except as noted above.

Bruce Rodda 7/14/07

BRUCE RODDA, Ph.D.

Rodda Deposition Exhibit 6

P's Exhibit ES

Marilyn J
Collicott /LAKE/PPRD/ABBOTT
02/27/2001 10.12 AM

To sthenault@rsi-nc.com
cc
bcc
Subject today's meeting

Hi Sheila

Attached are the handouts for todays meeting at3:00 CST.

agenda.pub Investigator tracking.xls R-Team scheduling.xls Subject-CRF Tracking xls

EXHIBIT
6

M99-114 INVESTIGATOR LIST

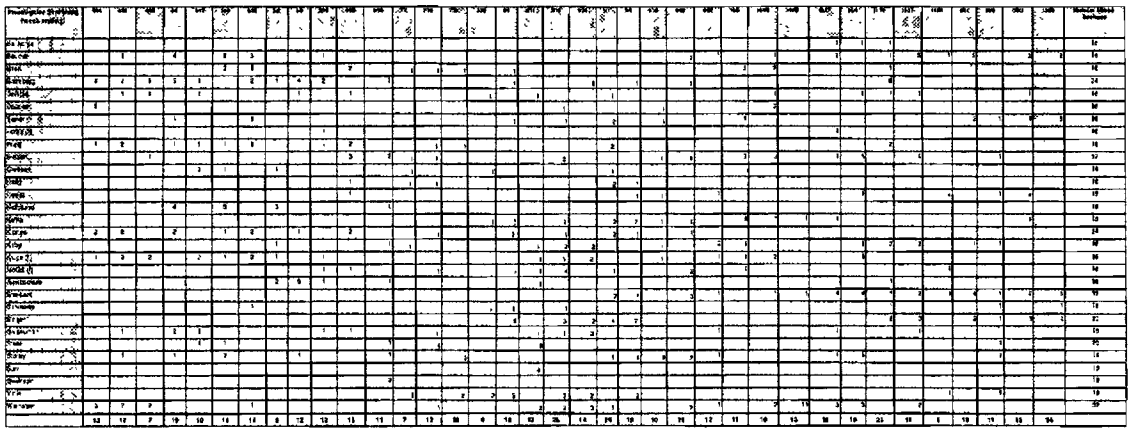
Investigator Last Name	Inv. #	State	Coordinator	Phone #	Total Screened	Total Randomized as of 1/04 11.46	Early Terms as of [illegible]	Completed Subjects as of [illegible]	CRFs In-House as of 2/27/01
Backonja	14272	WI	[illegible]	(608) 263-0170	4	3	1	2	3
Baumel (A)	7379	FL	Alfonso Moreno	(305) 865-0063	26	15	9	[illegible]	12
Baumel (B)	7379	FL	Janella Crasto	(561) 368-1123					
Brion	7396	AR	Donna Hemphill	(501) 227-5061	16	7	1	6	5
Bromberg	15844	UT	Donna Baum	(801) 586-6051	28	14	6	[illegible]	13
DeBold	15886	MN	Diane Whipple	(952) 993-2739	17	12	5	[illegible]	9
Drucker	15843	FL	[illegible]	(727) 725-8191	7	6	[illegible]	[illegible]	6
Eisner	15890	FL	Maggie Szymczak	(954) 720-1899	17	6	4	[illegible]	5
Forde (I)	15842	NY	Michael Belotto	(516) 496-6506	3	2	[illegible]	[illegible]	1
Fried	12999	RI	Thomas Ricci	(401) 467-7760	16	9	4	5	8
Gibson	15841	AR	[illegible]	(501) 227-7499	26	18	6	12	18
Gleason	15840	NM	[illegible]	(505) 262-7650	9	7	3	[illegible]	7
Haag	15839	MA	[illegible]	(413) 794-7252	8	6	4	2	6
Hewitt	14345	GA	Ellen McKinzie	(404) 778-3176	12	9	[illegible]	[illegible]	7
Holmlund	15838	NY	[illegible]	[illegible]	11	5	2	[illegible]	5
Kalka - A	12497	PA	[illegible]	[illegible]	16	7	4	[illegible]	7
Kipnes	15062	TX	[illegible]	(210) 615-6556	21	15	5	10	15
Kirby	9576	AZ	[illegible]	[illegible]	20	10	7	[illegible]	10
Kluge (I)	[illegible]	FL	[illegible]	(941) [illegible]	24	9	6	[illegible]	9
McGill (I)	15837	MO	Katherine Anderson	(314) 362-1404	17	8	2	[illegible]	5
Rowbotham	14368	CA	[illegible]	(415) [illegible]	13	4	1	[illegible]	4
Shaibani	16334	TX	George Manoukian	(713) 795-0033 x26	48	18	6	[illegible]	16
Simmons	15836	PA	Kathleen Hay	(717) 531-8694	7	6	4	[illegible]	5
Singer	16230	FL	Mercy Novero	(954) 433-5785	30	15	7	[illegible]	10
Sivakumar	15835	AZ	[illegible]	(602) [illegible]	14	9	4	[illegible]	9
Steel	15923	NC	[illegible]	[illegible]	10	8	[illegible]	[illegible]	8
Storey	14349	NY	Paula Levin	(518) 438-0922 press	21	13	[illegible]	[illegible]	3
Surf	16389	CA	[illegible]	[illegible]	4	3	[illegible]	[illegible]	3
Vinik	15834	VA	[illegible]	(757) [illegible]	16	6	[illegible]	[illegible]	6
Weinstein	13038	CA	[illegible]	(925) [illegible]	44	19	11	[illegible]	19
					505	269	132	[illegible]	234

Screen Failure Rate: 47%
Early Termination Rate: 49%
Completion Rate: 48%
Total Study Enrollment: 84%
CRFs In: 87%

All CRFs In

[FILE] [PAGE] [DATE][TIME]

Screen Tracking



M99-114 Early Terminations

Investigator	Subject #	Age	Days on Study Drug	Reason for Termination	Comments
Backonja	4467	37	1	AE	urea nitrogen level high panic at 56
Baumel	4145	85	1	AE	nausea, etc.
	4146	76	10	AE	dizziness, weakness, heart palpitations, headaches, blurred vision
	4147	85	11	AE	dizziness, weakness, sweating, blurred vision, heartburn, headache
	4228	73	unk	AE	hypoglycemic episode
	4231	73	27	AE	hallucinations
Biton	4260	82			
Bromberg	4113	69	10	AE	nausea, etc
	4115	45	5	AE	nausea, etc
	4117	50	7	AE	nausea, etc.
	4118	49	10	AE	dizziness, vomiting, nausea
	4125	85	1	AE	extreme nausea
DeBold	4051	71	9	AE	nausea, etc.
	4053	52	49	SAE	diabetic ketoacidosis
	4055	75	15	AE	int. nausea/vomit since 9/1, int abd bloating & constipation, decr urine stream since 8/26
	4057	72	16	AE	Intermittent nausea and vomiting
	4058		3	AE	dizziness, lethargy, vivid dreams, insomnia, increased neuropathic pain
	4060	67			
Drucker	4001	72	3 5	AE	joint pain in lower extremities
	4002	71	3	SAE	palpitations
	4003	78	0 5	AE	blurry vision
	4005	46			
	4008	72	1	AE	nightmares and intense neuropathic pain after 1st dose, whole body numb, wobbly, weak after 2nd dose
Eisner	4241	60	1	AE	nausea, etc.(went to ER)
Forde	4321	67	5	AE	disturbing dreams/anxiety
Fried	4063	66	14	SAE	syncopal episode related to historical atrial fib (admitted to hospital 5/30)
	4067	74	4	AE	diarrhea, GI upset, fatigue, light-headedness (patient took every dose following a meal)
	4069	61	8	AE	dizziness
Gibson	4354	73	1 5	AE	nausea
	4359	31	27	AE	nausea and vomiting
	4367	32	12	AE	nausea and vomiting
Gleeson	4164	51	1	AE	dizziness, disorientation
	4165	51			
	4167	70			
Haag	4337	43	5 5	AE	dizziness ~2hrs post-dose x 10 episodes
	4340	72	5	AE	difficulty falling asleep, awakening more frequently
	4341	85	36	AE	mental status changes
Hewitt	4311	52	8	AE	nausea and vomiting
Holmlund	4193	53	7	AE/SAE	vomiting, fatigue/ broken pelvis
	4195	60	7	AE	nausea, vomiting
	4197	62	4	SAE	chest pain
Kafka	4417	74	6	AE	nausea, vomiting
	CMW		7	AE	jaw pain, insomnia, increased BP, heart palpitations, tingling
	4419	61	46	AE	nausea and vomiting
Kipnes	4065	64	3 5	AE	nausea
	4066	55	25	AE	nausea
	4070	48	10	SAE	left arm pain
	4072	70	7	AE	nausea, etc.
	4075	74	2	AE	severe nausea, shakiness
Kirby	4178	62	9	AE	backache
	4501	55	9	AE	unsteady gait, nausea, indigestion
Kluge	4131	70	8.5	AE	nausea, etc
	4133	66	5 5	SAE	high blood glucose and chest pain due to GI problems (hospitalized 6/6-6/10)
McGill	4387	66	7	AE	nightmares, insomnia, nausea
	4390	59			
Shafiani	4450	56	30	AE	stomach ache
	4451	60	18	SAE	chest pain, shoulder pain
	4455	66	1	AE	got sick after first day
	4456	57	7	AE	headaches, lightheadedness, depression, rectal bleeding, sleeplessness caused by stomach acid

M99-114 Early Terminations

	4462	55	10	AE	vomiting, stomach sickness, diarrhea, fluttering, moaning, crying, shaking, confusion
	4463	68	6	AE	depressing dreams, LOE
	4493	51	13	AE	nausea, diarrhea, vomiting, headache
Simmons	4273	58	11	AE	GI sx, cognitive dysfunction, unusual dreams, bad taste in mouth, headache, bodyache
	4275	69	10	AE	vomiting, nausea, headache, vivid dreams, diarrhea, chills
	4276	56	19	AE	nausea
	4277	56	9	AE	nausea, vivid dreams
Singer	4401	53		AE	anginasecondary to coronary artery blockage
	4402	67	12	AE	dizziness, vomiting
	4403	57	25	AE	worsening insomnia
	4408	68	8	AE	vomiting
Sivakumar	4036	59	3 5	AE	nausea, etc.
	4040	57	7	AE	apprehensive, irritable, tinnitus, headache, burning eyes, diarrhea, vivid dreams
	4041	51	1	AE	nausea, vomiting, diarrhea
Steel	4209	68	22	AE	light-headed, dizzy
	4210	73	9	AE	vomiting
	4215	60	10	AE	severe nausea
	4216	52			
Storey	4098	70	6 5	AE	nausea, etc.
	4100	56	3	AE	nightmares
	4102	69			
Weinstein	4020	73			
	4021	65	13	AE	coughing, sore throat, cold sx (went to ER)
	4024	63			
	4489	79	6	AE	dizziness, nausea, diarrhea

	82	63.2	10 3		
Baumel	4227	57	unk	Other	withdrew consent due to elective surgery
	4236	56	7	Other	withdrew consent
Bromberg	4126	65	6	Other	subject randomized prior to reviewing baseline diary, diary scores too low, subject never dosed
DeBold	4058	28	82	LOE	
Fried	4066	58	20	LOE	
Gibson	4355	44	33	Other	took anti-inflammatory drug for hand pain
	4357	71	6	Other	had facets injected for pain
Harris	4306	60		Other	withdrew consent
Kirby	4179	49		Other	wanted to start narcotics for pain control
	4180	50		Other	history of alcoholism
Shaibani	4453	63	8	LOE	
Singer	4404	60	17	LOE	
	4405	64	20	Other	took naprosyn for knee pain
	4410		21	Other	moving out of state
Sivakumar	4035	50	27	Other	began exclusionary meds
Steel	4214	57	8	LOE	
Weinstein	4018	66		Other	withdrew consent
	4026	70	unk	Other	lost to follow-up
	4004	71	19	LOE	
	4032	73	14	LOE	
	13	59.2			
TOTAL	95				

Rodda Deposition Exhibit 2

Summary of Anticipated Expert Testimony

by

Dr. Bruce E. Rodda

The following is a summary of the anticipated expert testimony of Dr. Bruce E. Rodda in connection with the action entitled John Hancock Life Insurance Company, John Hancock Variable Life Insurance Company, and Manulife Insurance Company (f/k/a Investors Partner Insurance Company) v. Abbott Laboratories, U.S.D.C. (Mass.) Civil Action No. 05-11150-DPW. Dr. Rodda has been asked by Munger, Tolles & Olson LLP, on behalf of Abbott Laboratories, to provide the Court with expert testimony regarding the development of new pharmaceutical compounds, including without limitation, the statistical aspects of evaluating and interpreting the results of clinical trials in support of these developmental activities. Dr. Rodda's testimony may include, inter alia, expert testimony regarding the Abbott study referred to as ABT-Protocol M99-114, A Randomized, Double-Blind Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy.

26 Feb 07

A summary of Dr. Rodda's training and experience can be found at pages 1-3 of the Summary of Anticipated Expert Testimony by Dr. Bruce E. Rodda served on plaintiffs on January 19, 2007.

This summary of Dr. Rodda's anticipated testimony is expected to include opinions regarding the anticipated testimony of Dr. Barry Gold with regard to statistical issues, the anticipated testimony of Dr. William Fairweather, the clinical protocol and clinical study report for Abbott study ABT-M99-114, and various statistical topics associated with clinical development generally and study ABT-M99-114 in particular.

Dr. Rodda will testify based upon his own experience, using information and materials available in the public domain (including, but not limited to, information from the United States Food and Drug Administration's ("FDA") website and the European Medicines Agency ("EMEA") website), and upon testimony and materials obtained in discovery in this action. During his testimony, Dr. Rodda may make reference to specific evidence contained in documents or witness testimony.

The opinions and analysis contained in this summary of Dr. Rodda's anticipated testimony are based on currently available information. Dr. Rodda's work is continuing and he plans to analyze any new information. Dr. Rodda may modify this summary in light of such new information. The present summary of Dr.

Rodda's anticipated testimony may be supplemented by his deposition testimony.

Dr. Rodda is expected to opine on Dr. Gold's and Dr. Fairweather's anticipated testimony regarding the statistical considerations for Protocol M99-114 and the outcome of that study. He may opine on areas in which he feels either Dr. Gold's anticipated testimony or Dr. Fairweather's anticipated testimony is incorrect, incomplete, or unclear. Some of the comments that Dr. Rodda is expected to make in this regard are as follows.

Dr. Rodda's anticipated testimony may be grouped into three related areas – general considerations, power and sample size considerations, and results and conclusions regarding Study M99-114.

GENERAL – Dr. Rodda may opine that the underlying approach to designing and evaluating a comparative clinical trial is to assume, at the outset, that the treatments under investigation do not differ in their response. This is referred to in statistical terminology as the "null hypothesis". The study is then conducted with the objective of collecting information that will refute this hypothesis if the experimental treatment is, in fact, superior to the control treatment. If a substantial difference favoring the experimental treatment is observed when the study is completed, the conclusion would be that the experimental treatment is superior to the control. On the other hand, if a small difference was observed

that was not inconsistent with the null hypothesis of no difference between the treatments under study, the conclusion would be that any real difference between the experimental and control treatments was too small to be of clinical importance. In the context of Abbott study M99-114, this means that Abbott planned Study M99-114 with the expectation that ABT-594 was superior (and not equal) to placebo. Abbott designed Study M99-114 to have a high likelihood of producing results that would support the conclusion that ABT-594 was superior to placebo if, in fact, ABT-594 was truly superior. The results of M99-114 provided a substantial difference between each of the three doses of ABT-594 and placebo with respect to the primary variable (Likert pain scale), clearly confirming the superiority of each of the three doses of ABT-594 compared with placebo.

The results of a clinical trial are analyzed by statisticians to provide a basis for reaching conclusions. In his anticipated testimony (p. 15, line 16) Dr. Gold states that after data are "sorted into groups by dose and drug, one or more statistical tests will be applied." Dr. Rodda is expected to provide expert opinion that when the study is completed and the data have been unblinded, the statistical team will perform a complete statistical evaluation of the study results based on a statistical analysis plan (SAP) that was designed prior to unblinding the clinical data. This plan for the statistical analysis will sometimes be included in the body of the protocol or may be written as a standalone document for complex studies. If a standalone SAP is written, it is often appended to the protocol. The statistical

analysis will be performed in concert with clinical experts and will be far more extensive than "one or more statistical tests".

With regard to Dr. Gold's anticipated testimony (page 5, line 4) Dr. Rodda may opine that Dr. Gold's use of the term "statistically evaluate" is unclear. Dr. Rodda is expected to discuss that while statistical concepts and techniques are important for the evaluation of safety and efficacy, there are other essential sources of input, e.g., clinical knowledge and experience that are essential in the evaluation of clinical trials.

POWER AND SAMPLE SIZE – Every clinical trial is different and the outcome of each clinical trial is unpredictable. If the identical trial were conducted many times, the results would differ each time for a variety of reasons. In addition to the uncertainty caused by random variation, other factors affect the confidence we have in the inferences made at the conclusion of a study. Some of these factors are the variability of the basic measurement, the size of the true difference between the experimental treatment and control (which is unknown and must be estimated from the study), the probability with which one wishes to detect a true difference if it exists (power), the risk one is prepared to take in declaring a true difference exists when it does not (Type I, or alpha, error), and the number of patients participating in the study.

For example, to estimate the sample size for Protocol M99-114, Abbott used information from Protocol M98-833. That study suggested that a meaningful difference would be 11.4 units on a 100 point Likert scale with an associated standard deviation of 24.4 units, yielding a standardized difference (or treatment effect) of 0.46. Abbott utilized this standardized effect size, a power (or probability of getting a statistically significant outcome if the anticipated difference was real) of at least 0.8, and an acceptance of a 5% risk of falsely declaring ABT-594 superior to placebo, resulting in a planned sample size of approximately 80 patients in each group.

Dr. Rodda is also expected to testify that power is a concept that is only relevant for planning a clinical trial and is of little value in the interpretation of the results of a study.

Organizations sponsor clinical trials because they believe that their experimental treatment will have a clinically important difference over the standard treatment or a negative control. When a sponsor commits to performing a clinical trial, the sponsor wants to minimize the likelihood that the study will be inconclusive. Said differently, if the new treatment has a clinically important effect of Δ, the sponsor wants the study to have a high likelihood (or power) of demonstrating that effect with a "statistically significant" result. That is, the sponsor does not want the study to result in a conclusion of "ineffective" or "inconclusive" if the product really is superior to the control. Intuitively, because a larger trial provides more

information than a similar smaller trial, a larger trial will be more likely to be conclusive than a smaller trial. Because clinical trials are very expensive, it is critical that studies be designed with the proper number of patients to satisfy their goals. Too many patients will result in unnecessary exposure of patients to experimental treatments and will be unnecessarily expensive. Too few patients, on the other hand, may result in an inconclusive study with the potential need to repeat it. For these reasons, a clear strategy must be followed for determining the number of patients required in a clinical trial.

Four basic factors influence the size of a clinical trial.

Variability – If an effect is associated with very small variability (i.e. the effect is very consistent), few subjects would need to be evaluated in a clinical trial to have confidence regarding any decisions made about the particular effect of interest. In contrast, if the effect is quite variable or inconsistent, conclusions based on the information provided by the same few patients would be less convincing. To provide the additional information necessary for similar confidence in the two cases, more patients must be evaluated when there is greater variability. For any scientific measure, precision increases and the likelihood of error decreases with additional information. In the clinical trial context, this information corresponds to a decrease in variability and/or an increase in the sample size.

Clinically Important Difference between the Experimental and Control Treatment - The second factor that influences the size of a study is the difference between the experimental treatment and the control that is clinically important. If the true (but unknown) difference between the comparative agents is very small, the study will require a large number of patients to provide adequate evidence to conclude that the specified difference is not zero as stated in the null hypothesis, but that a real difference exists between the treatments. On the other hand, if the sponsor believes that its new product is superior to the standard by a substantial margin, fewer patients will be required to obtain a statistically significant result if the true difference between the two treatments is large.

Risk of a False Positive Conclusion - The third consideration influencing the size of a clinical trial is the probability of falsely concluding the new treatment is superior when it is not. Consider that even if the experimental treatment and control treatment had inherently identical effects, the results of any specific study could randomly favor the experimental treatment to a degree that the (incorrect) conclusion would be that the experimental treatment is superior to the control treatment. This probability is also called a Type I error or alpha error (also referred to as the level of statistical significance) and is chosen before the study begins. At the conclusion of the study, the null hypothesis is tested against this alpha error standard (e.g. $p<0.05$), and if the results of the study are more extreme than would be expected if there were no true therapeutic difference, the result would be called "statistically significant (at the $p<0.05$ level)" and the

conclusion would be that the experimental treatment is effective. The probability of making this conclusion in error would be 0.05 (or 1/20) in this example.

The Type I error is usually set at 0.05 (or 5%) and this is a standard recommended by the FDA and other regulatory agencies. Hypothesis tests routinely use this cutoff as the definition of "statistical significance". In the present study, the alpha level was chosen to be 0.05 and was specified in the protocol. At the conclusion of Study M99-114, the results of comparing each dose of ABT-594 with placebo were "statistically significant" ($p<0.05$), implying that each dose is truly superior to placebo with respect to pain.

Risk of a False Negative Conclusion/Power – It is also possible to incorrectly conclude that a clinically important effect is absent. Suppose that the experimental treatment is truly superior to the control treatment by, say Δ units. The results of any study are unpredictable, and even though the experimental treatment is, in fact, superior to the control treatment, the outcome of a particular study might result in a difference that was quite small, just by chance. In that case, the test of the null hypothesis would not be rejected (that is p would be greater than 0.05), and the incorrect conclusion would be that the experimental treatment is not superior to the control treatment. This type of error is referred to as Type II error or Beta error. The probability of correctly concluding that the experimental treatment is superior to the control is one minus the probability of incorrectly concluding the treatment is effective. The probability of correctly

concluding the experimental treatment is superior is termed "power". Sponsors and investigators usually want this probability to be quite high and often select sample sizes that will provide 80% power. In study M99-114, the planned power was 80% power.

The relationships among the various factors contributing to the estimation of the sample size may be clearer by considering the following equation:

$$n = \frac{2(z_{\alpha/2} + z_{\beta})^2 \sigma^2}{\Delta^2}$$

where: n is the sample size in each treatment group and

$z_{\alpha/2}$ is an index of the risk of a false positive – the higher $z_{\alpha/2}$, the lower the risk (1.96 in Study M99-114)

z_{β} is an index of the risk of a false negative – the higher z_{β}, the lower the risk (0.84 in Study M99-114)

σ is the standard deviation – the measure of variability (σ = 24.4 from Study M98-833)

Δ is the difference the study is designed to detect (Δ=11.4 from Study M98-833) (Note that Δ/σ =0.46 is the standardized treatment effect Study M99-114 was designed to detect).

Note that the z-values above are values of standard normal deviates and are indexes of the probabilities; they do not represent the actual probabilities.

Dr. Rodda is expected to opine that the sample size for the Protocol M99-114 was estimated using a standard statistical approach for the comparison of two means. While there are usually several choices that may be appropriate for

estimating the sample size in any clinical trial, the procedures used in this study were consistent with good statistical practice and the sample size was appropriate for detecting the pre-specified standardized treatment effect of 0.46 in the primary variable with 80% power at an alpha level of 0.05.

It should be understood that just because a sample size has been chosen which appears to provide 80% power, it does not imply that there is an 80% chance that a given trial will be successful. Power is a concept that is only relevant for planning a clinical trial and is of little value in the interpretation of the results of a study.

Even if the planning has been appropriate and the calculations are correct consider the following points.

1. The assumptions used to estimate the sample size are approximations. The estimate of variability used in the calculation of sample size is derived from previous experience, often in a different environment than the given study. The variability that will actually occur in the planned study may be greater or less than used in the power calculations. In this case situation, the power would be lower or higher than anticipated.

2. The true difference between the treatments is unknown and the study may result in a higher or lower difference than that used to estimate the sample size.

3. The new treatment may not actually be superior. (In fact, if a study correctly results in this conclusion, the study has not been a failure. The study has reached the correct conclusion, even though it was not the conclusion that was desired.)

4. Even if the new treatment is superior, the difference actually seen in a particular study may not be conclusive, just by chance.

Dr. Rodda will be prepared to discuss the concept of power as it relates to estimation of sample size and how this is a quantifiable risk chosen at the discretion of the sponsor. He will also be prepared to discuss the fact that neither "power", nor "statistical significance" is associated with the validity of a study. The validity of a study is dependent on its design and implementation. Two studies of the same design but of different sizes will both be equally valid if they are properly designed and executed. The larger study will provide more information and precision regarding the conclusions than the smaller study, but they can be equally valid.

In Dr. Gold's anticipated testimony (page 8, line1 and preceding), he states that variability is an important factor in the determination of the size of a study. Dr. Rodda is expected to opine that sample size is not determined solely by making certain assumptions about variability in the data. Sample size is also dependent

on three other considerations as described previously: the risk (probability) of declaring an ineffective treatment to be effective at the conclusion of a study, the risk of not detecting a true clinically important difference at the conclusion of the study (and thereby erroneously concluding that an effective treatment is ineffective), and the magnitude of the clinically important treatment effect the study is designed to detect.

While Dr. Gold's contention (page 8, line 3) that the statistician's duties typically include estimating "very closely" how many patients must be enrolled, the term "very closely" is not correct. Dr. Rodda is expected to opine that estimating sample size is dependent on both the clinically important difference and the estimated variability of response, in addition to the considerations regarding false positive and false negative errors presented previously. The variability used in estimating a sample size is often an estimate from other studies and the estimated sample size is only as good as the estimate of the variability used to calculate it.

Beginning on page 8, line 5 of his anticipated testimony, Dr. Gold states that the "power of a study refers to the statistical test they have chosen and the probability that the test will fail to detect a true difference between two groups." Dr. Rodda is expected to opine that the "power" of the study is not only a function of the test to be used in the analysis of the primary variable, but more importantly, refers directly to the probability that the study, as designed, will find

the pre-specified clinically important difference to be statistically significant at a pre-specified risk of a false positive outcome (declaring an ineffective drug to be effective). It is not, as Dr. Gold states, the probability of failing to detect a true, pre-specified, difference; it is the probability of actually detecting that difference. In addition, it is not the statistician who wishes to detect the difference; it is the sponsor, through the project team (and often following discussions with the FDA), who defines the pre-specified difference and is most interested in the outcome.

RESULTS AND CONCLUSIONS OF THE M99-114 STUDY– Dr. Rodda is also expected to testify that both the International Conference on Harmonization (ICH) and the U.S. Food and Drug Administration (FDA) recommend using as complete a dataset as possible for evaluating both safety and efficacy. Any patient that can be evaluated for efficacy should be included in the primary analysis. The analytic approach proposed for protocol for study M99-114 is consistent with the intent of this guidance. In fact, the protocol states that "all subjects receiving at least one dose of study drug with at least one diary-based baseline and at least one post-baseline pain assessment for the diary-based Pain Rating Scale will be included in the intent-to-treat analysis." The description of this dataset is included in the protocol and was defined before the study was begun. This dataset is consistent with ICH E-9 (Statistical Principles for Clinical Trials) which describes such a dataset as being "as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects." The clinical study report for Protocol M99-114 includes 225 of the 266 patients

randomized to treatment in the primary efficacy analysis; all 266 patients are included in the safety analysis.

Patients withdraw from clinical trials for many reasons. Some are random and do not influence or bias the conclusions. However, patients may withdraw from clinical trials for two primary reasons that may be related to the treatment they receive - the adverse events they experience are such that they no longer wish to participate in the study or the treatment they are receiving is insufficiently effective to support their continued participation in the study. In either case, patients who withdraw from a study provide valuable information regarding the safety and efficacy of the product under investigation. Excluding patients from the analysis of clinical trials can substantially bias the conclusions reached. It is for this reason that both ICH guidelines and the FDA recommend using all patients with valuable data in the analysis of safety and efficacy. In reviewing the documentation of Abbott's deliberations prior to terminating enrollment, there was never a reference to using less than all evaluable patients in the appropriate analyses. Dr. Rodda may opine that given the above, Dr. Fairweather's position of considering only 137 patients for evaluation is scientifically inappropriate and inconsistent with ICH and FDA standards. To use only the 137 completing patients as Dr. Fairweather suggests would not be consistent with good scientific practice, would bias the results in favor of ABT-594, and would not be acceptable to the regulatory and scientific community.

Documents relating to internal meetings at Abbott suggest that Abbott became aware at some point that they would not meet the enrollment goals in the planned enrollment period for Study M99-114. During the period preceding Abbott's decision to terminate enrollment, several activities took place in an effort to determine the impact of these factors on the probability that the study would satisfy its goal of distinguishing ABT-594 from placebo. In addition to efforts targeted at improving enrollment, Abbott evaluated the effect of smaller sample sizes on the probability (power) of detecting their predefined standardized treatment effect of 0.46. This was done in a fully blinded manner and assumed that all patients would be evaluable for efficacy. This activity focused on the following question: if the study concludes with a reduced number of patients, what is the probability (power) of detecting (finding statistically significant, $p<0.05$) the proposed treatment effect of 0.46 between ABT-594 and Placebo? An example of the power considerations of this evaluation is contained in a memo from Mr. James Thomas to Ms. Rebecca L. Brown on 9/28/2000 in preparation for a meeting on the topic. This table is reproduced in part below.

Option	Sample Size	Effect	Power
1	20	.46	0.29
2	25	.46	0.36
3	30	.46	0.42
4	35	.46	0.48
5	40	.46	0.53
6	45	.46	0.59
7	50	.46	0.62
8	55	.46	0.67
9	60	.46	0.71
10	65	.46	0.74
11	70	.46	0.77
12	75	.46	0.80
13	80	.46	0.82

Entries in this table include possible sample sizes (per group), the hypothesized treatment effect Study M99-114 was designed to detect and the power to detect this difference for each sample size. It can be seen from this table that the actual number of patients at the termination of enrollment (266 or about 65 per group) would provide 74% power to detect the hypothesized 0.46 treatment effect (compared with an initial power of at least 80% as cited in the protocol). This activity provided Abbott with a full understanding of the probabilities of Abbott's detecting their chosen effect for several smaller sample sizes. However, if the true treatment effect was larger than 0.46, the probability of finding this larger difference with the reduced sample size would increase.

It is common in clinical trials for actual enrollment to be less than planned. The only risk of stopping enrollment in a study with fewer patients than planned (as it relates to power) is that the treatment difference between the experimental agent and the control agent may not be statistically significant. In these cases, the

sponsor may accept that the study's power to detect the originally hypothesized difference may be lower than used in estimating the study's size. There are several strategic considerations that may affect the sponsor's decision. Extending a study for an additional year, for example, to acquire the planned sample size may increase the cost to an unacceptable degree or expose the product to a new competitive agent such that the higher risk of extending the study may be unacceptable to the sponsor. In addition, after the study has begun, factors such as safety considerations with the new treatment or the introduction of a new competitor may require that a successful product possess a larger superiority over the control treatment than was originally planned. In this case, a reduced sample size may be consistent with a comparable, or perhaps greater, power than originally planned, since larger effects require smaller sample sizes.

Dr. Fairweather opined that of the 266 patients enrolled in this study, only 137 were "usable". This suggests that the remaining patients provided no information regarding the safety and efficacy of ABT-594. As stated earlier in this summary, those patients who withdraw from a clinical trial provide important information regarding the safety and efficacy of the products under study. ICH guidelines and the FDA would demand that all relevant information be used in the analysis; patients who withdraw cannot be considered "unusable" for either safety or efficacy. In addition, if one were to accept Dr. Fairweather's contention regarding usability, the original sample size of 320 patients would need to be increased by

a factor of 266/137 (1.94), to a total enrollment of 621 patients to net 320 "usable" patients.

Dr. Rodda may opine that although Abbott terminated enrollment before reaching the target of 320 patients, Abbott carefully evaluated the possible outcomes of the study based on the reduced sample size and concluded that the reduced power associated with the originally hypothesized treatment effect was acceptable. Referring to the table above, Abbott knew that its power to detect their original hypothesized treatment effect of 0.46 would be approximately 74%, rather than the planned 80%. Viewed somewhat differently, while the initial plan had an 80% power to detect a treatment effect of 0.46, the actual intent-to-treat sample of 225 patients (Clinical Study Report, Table 11.4a) had an 80% power to detect a treatment effect of 0.56. Since the actual differences observed between the active treatment groups and the placebo group were all in the range of 0.8 to 0.9 units on the 11 point Likert scale (and were all statistically significant at the $p<0.05$ level), the study clearly had adequate power to address the primary objective of the study, and the study should be considered conclusive (successful) in this respect.

Although Abbott did not know the margin by which ABT-594 would be superior to the control when Abbott decided to terminate enrollment in this study, that margin was substantially larger than originally anticipated. This difference was manifested in results that were statistically significant, rendering the question of

adequate power (i.e. the probability of obtaining a statistically significant result) moot. Although both Dr. Gold and Dr. Fairweather had comments regarding the effective sample size of study M99-114, neither questioned that the study was conclusive in demonstrating that ABT-594 was superior to placebo with respect to the primary efficacy variable, despite a sample size that was somewhat less than originally planned.

References

1. European Medicines Agency: Scientific Guidelines for Human Medicinal Products: ICH E6 – Guideline for Good Clinical Practices. 1996.
2. European Medicines Agency: Scientific Guidelines for Human Medicinal Products: ICH E9 – Statistical Principles in Clinical Trials. 1998.
3. The World Medical Association: World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 2004
4. 21 CFR 312.40 General requirements for use of an investigational new drug in a clinical investigation
5. Abbott communiqué Dr. James Thomas to Ms. Rebecca L. Brown – 9/28/2000
6. Summary of proposed expert testimony by Dr. Barry I. Gold
7. Summary of proposed expert testimony by Dr. William R. Fairweather

Documents Reviewed by Dr. Bruce Rodda

Bates Nos.	Date	Description
-----	10/13/06	Expert report of Barry I. Gold
-----	01/19/07	Expert report of Dr. William R. Fairweather
-----	6/23/06	Supplemental Complaint
-----	2/6/06	Hancock's Objections & Responses to Abbott's First Set of Interrogatories
-----	9/27/06	Marilyn Collicott deposition transcript
ABBT 0004410-0004415	4/00/00	Collicott Exhibit 6
ABBT 0004436	8/00/00	Collicott Exhibit 10
ABBT 0004443-0004447	9/00/00	Collicott Exhibit 12
ABBT 0004448-0004454	10/00/00	Collicott Exhibit 15
ABBT 237155-237159	10/9/00	Collicott Exhibit 16
ABBT 0004455-0004459	11/00/00	Collicott Exhibit 17
ABBT 0004460-0004464	12/00/00	Collicott Exhibit 22
ABBT 0000322-0000327	1/00/01	Collicott Exhibit 27
ABBT 240624	1/8/01	Collicott Exhibit 28
ABBT 242693-242699	1/16/01	Collicott Exhibit 29
ABBT 0001748-0001758	4/23/01	Collicott Exhibit 39
ABBT 335154	5/4/01	Collicott Exhibit 41
ABBT 239029	5/18/01	Collicott Exhibit 42
ABBT 240374-240412	10/15/02	Collicott Exhibit 49
-----	9/29/06	Bruce McCarthy deposition transcript and all exhibits
ABBT 0020894-967	10/99/99	Draft 10/7/99 M99-114 Protocol
ABBT 0065818-0078893	-----	CD containing: Clinical Study Report and Clinical Protocol
-----	-----	CD containing: Amendment for Study M99-114
ABBT 159274	9/3/99	Email to Waleska from Siber
ABBT 51889	12/21/99	Email to Siebert from Thomas
ABBT 65818-65896	2/8/00	Protocol M99-114
ABBT 242154	5/25/00	Letter to Hoffstetter from Collicott
ABBT 33462-33467	5/31/00	Site breakdown/enrollment for M99-114
ABBT 79825-79826	6/20/00	Emails between Nunn and Thomas
ABBT 241296-241297	6/27/00	Emails among McCoy, Rowbotham and Collicott re barrier to enrollment
ABBT 161395	7/6/00	Email to Matalonis, et al from Garavalia
ABBT 82516	7/7/00	Email to Morris, et al from McCarthy
ABBT 239985-239988	7/10/00	Site breakdown/enrollment for M99-114
ABBT 83022	7/13/00	Email to Landsberg, et al from Collicott
ABBT 161644-161645	7/25/00	Emails among Biarnesen and Powers
ABBT 78935-78941	8/7/00	Email to Thomas from Hansen with patient listing
ABBT 335227-335307	8/23/00	ABT-594 Development Plan
ABBT 80232-80237	8/29/00	Email to Kacos from Thomas with data for power curves
ABBT 241302	8/31/00	Letter prototype to investigators from Collicott
ABBT 51907-51908	9/28/00	Power calculations

ABBT 82259	9/28/00	Email to Brown from Thomas with power calculations
ABBT 51892-51905	9/28/00	Email to Brown from Thomas with power calculations
ABBT 233741-233749	9/28/00	CT Recruitment and Centralized Screening Program
ABBT 237155-237159	10/9/00	Email to Nunn from Collicott with investigator tracking list
ABBT 107607-107609	10/30/00	Email to Biarnesen from Silber with list of project review questions
ABBT 109399-109400	11/22/00	Email to Morris from McCarthy with items for meeting discussion
ABBT 241843-241847	11/28/00	Email to Schanzenbach from Collicott
ABBT 81606	11/29/00	Email to Kacos from Thomas with confidence intervals for difference
ABBT 242373	12/6/00	Email to Biarnesen from Collicott re randomization goals
ABBT 233539-233540	12/14/00	Email to Schanzenbach from Collicott "decided to end enrollment as of 1/5/01
ABBT 240624	1/8/01	Email to Schanzenbach from Collicott
ABBT 81459-81460	1/12/01	Email to McCarthy from Thomas with adverse event experience
ABBT 233000	1/15/01	Email to Schanzenbach from Collicott
ABBT 242693-242699	1/16/01	Meeting agenda with tables of investigators and early terminations
ABBT 8169-8176	Feb 2001	Descriptive memo on marketing prospects
ABBT 246076-246084	Feb 2001	Descriptive memo on marketing prospects
ABBT 242650	2/5/01	Tracking report
ABBT 242503	2/12/01	Tracking report
ABBT 242681-242688	2/13/01	Meeting agenda with tables of investigators and early terminations
ABBT 237944	2/20/01	Tracking report
ABBT 233001	2/26/01	Email from Brownell to Collicott re tracking report
ABBT 238329-238335	2/27/01	Meeting handouts with tables of investigators and early terminations
ABBT 298380-298385	3/5/01	Meeting minutes: Pain Strategy Decision Analysis
ABBT 297530-297555	3/7/01	Abbott Portfolio Review
ABBT 238328	3/13/01	Tracking report
JH 8074-8211	3/13/01	Research Funding Agreement by Hancock and Abbott
ABBT 240978	3/20/01	Tracking report
ABBT 79111-79119	5/23/01	Adverse event experience tables
ABBT 241331-241560	7/31/01	M99-114 Analysis
ABBT 241298-241300	8/14/01	Study enrollment graphs
ABBT 80451	2/19/02	Email to Olson from Thomas "screening failure rate 47%"
ABBT 79395	3/6/02	Email to Biarnesen from Thomas indicating blind broken 4/23/01
ABBT 51885-51888	-----	Power curves
ABBT 155581-155587	-----	Initial Portfolio Prioritization

JH8153 – JH8210	February 2001	Descriptive Memoranda
ABBT0104016-0104017	11/21/00	Email from McCarthy to Silber
ABBT01214045-1214046	12/18/00	Email from Biarnesen to Robinson
ABBT0122646-0122718	11/17/00	ABT-594 Project Review